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Hypertension in Relation to Dioxins and Polychlorinated Biphenyls from the Anniston Community Health Survey Follow-Up

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Background: In 2014, we conducted a longitudinal study [Anniston Community Health Survey (ACHS II)] 8 y after the baseline (ACHS I).

Objectives: We investigated the relationship between persistent chlorinated compounds and hypertension in residents living around the former polychlorinated biphenyl (PCB) production plant in Anniston, Alabama. We also examined the potential role of inflammatory cytokines in those with hypertension.

Methods: A total of 338 participants had their blood pressure measured and medications recorded, gave a blood sample, and completed a questionnaire. Prevalent hypertension was defined as taking antihypertensive medication or having systolic blood pressure >140 mmHg and/or diastolic pressure >90 mmHg; incident hypertension used similar criteria in those who developed hypertension since the baseline in 2005–2007. PCB congeners were categorized into structure–activity groups, and toxic equivalencies (TEQs) were calculated for dioxin-like compounds. Descriptive statistics, logistic and linear regressions, as well as Cox proportional hazard models, were used to analyze the associations between exposures and hypertension.

Results: Prevalent hypertension (78%) in ACHS II showed statistically significant adjusted odds ratios (ORs) for PCBs 74, 99, 138, 153, 167, 177, 183, and 187, ranging from 2.18 [95% confidence interval (CI): 1.10, 4.33] to 2.76 (95% CI: 1.14, 6.73), as well as for two estrogenic-like PCB groups, and the thyroid-like group [ORs ranging from 2.25 (95% CI: 1.07, 4.75) to 2.54 (95% CI: 1.13, 5.74)]. Furthermore, analysis of quartiles demonstrated a monotonic relationship for dioxin-like non-ortho (non-*o*)-PCB TEQs [fourth vs. first quartile: 3.66 (95% CI: 1.40, 9.56)]. Longitudinal analyses of incident hypertension supported those positive associations. The results were strongest for the di-*o*-PCBs [hazard ratio (HR) = 1.93 (95% CI: 0.93, 4.00)] and estrogenic II PCB group [HR = 1.90 (95% CI: 0.96, 3.78)] but were weaker for the dioxin TEQs.

Discussion: Findings supportive of positive associations were reported for dioxin-like mono-*o*- and non-*o*-PCBs as well as for nondioxin-like estrogenic and thyroid-like congeners with prevalent and incident hypertension, suggesting that multiple pathways may be involved in hypertension development. https://doi.org/10.1289/EHP5272

Introduction

Hypertension is one of the leading risk factors for death and disability globally, according to the World Health Organization Global Burden of Disease Study (Forouzanfar et al. 2017). In 2008, the global prevalence of hypertension (high blood pressure) rose to 1 billion people, which accounts for 40% of adults at least 25 years of age (WHO 2013). Of the 17 million deaths attributed to cardiovascular disease worldwide, hypertension accounts for 9.4 million, including 45% of heart disease and 51% of stroke-related mortalities (WHO 2013). In the United States, the overall prevalence of hypertension among adults aged 18 and over was 29% in 2012 (Nwankwo et al. 2013).

There are a number of established risk factors for developing hypertension, including those linked to heredity and certain modifiable risk factors that can be changed to prevent or control hypertension. Known risk factors for hypertension include genetics/family history, age, race, and gender. Modifiable risk factors include obesity, diabetes, high salt and fat intake, harmful levels of alcohol use, physical inactivity, high cholesterol, sleep apnea, and poor stress management (AHA 2016). Poor lifestyle behaviors, socioeconomic factors, genetics, and environmental exposures have also been studied extensively in assessing the causes and consequences of hypertension (Cuschieri et al. 2017; Dickson and Sigmund 2006; Park et al. 2016).

Persistent organic pollutants (POPs), including polychlorinated dibenzo-*p*-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), organochlorine pesticides, and polychlorinated biphenyls (PCBs) (Jones and de Voogt 1999), have been the focus of several reviews that examined links between hypertension/heart disease and chemical exposure (Humblet et al. 2008; Everet et al. 2011; Lind et al. 2014; Faroon and Ruiz 2016; Perkins et al. 2016; Song et al. 2016). A recent meta-analysis of epidemiologic studies assessing the impact of POPs on hypertension and cardiovascular disease revealed that the dioxin-like compounds (including dioxin-like PCBs) significantly increases the risk of hypertension (Park et al. 2016).

Nondioxin-like PCB groups such as estrogen-like PCBs (Warner et al. 2012) could also play a role in hypertension since female sex hormones may protect against cardiovascular disease by acting as antiandrogens (Masi et al. 2006; Freire et al. 2014). Another PCB group that may impact hypertension is thyroid-like congeners because both hyperthyroidism and hypothyroidism produce changes in cardiac contractility and blood pressure (Marvisi et al. 2013).

Most studies analyzing the connection between PCBs and hypertension are cross-sectional (Everett et al. 2008; Goncharov et al. 2011; Henríquez-Hernández et al. 2014; Yorita Christensen and White 2011; Peters et al. 2014) as are those linking dioxin-like compounds and hypertension (Chang et al. 2010; Ha et al. 2009; Ilhan et al. 2015; Lee et al. 2007; Uemura et al. 2009; Nakamoto et al. 2013). Cohort studies have been used infrequently, with only a few conducted to assess POPs and hypertension incidence

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(Arrebola et al. 2015; Donat-Vargas et al. 2015, 2018; Raffetti et al. 2018).

Immunotoxic and potentially pro-inflammatory properties of dioxin-like compounds have long been known to affect different components of the immune system (Hennig et al. 2002; Kerkvliet 2012). The immune system and systemic inflammation have also been suspected to play an important role in the biology of atherosclerosis (Ross 1999; Hansson 2005; Helyar et al. 2009). Inflammatory cells and signals drive the healing response to vascular injury, allowing the initiation and growth of atherosclerotic plaque and contributing to the development of hypertension (Norlander et al. 2018; Ridker et al. 2017). When endothelial cells are exposed to PCBs or dioxin-like compounds, inflammatory pathways may be activated, leading to the expression of cytokines (Pacher et al. 2002; Hennig et al. 2007; Helyar et al. 2009; Liu et al. 2015). Inflammatory cytokines released from these cells, including interleukin 1-β (IL-1β), IL-17, interferon gamma (IFN-γ), tumor necrosis factor-α (TNFα), and IL-6, promote both renal and vascular dysfunction and damage, leading to enhanced sodium retention and increased systemic vascular resistance and atherosclerosis (McMaster et al. 2015; Norlander and Madhur 2017; Norlander et al. 2018).

The Anniston Community Health Survey (ACHS I; 2005–2007) was conducted in Anniston, Alabama, to assess potential health impacts of living in close proximity to a chemical plant that produced PCBs from 1929 to 1971 (Pavuk et al. 2014a). The study revealed a significant association between hypertension prevalence and the sum of 35 PCB congeners among participants not taking antihypertensive medication (Goncharov et al. 2010). Various di-, tri-, and tetra-ortho (*o*)-PCBs also were linked to systolic and diastolic blood pressure levels (Goncharov et al. 2011). Association between chlorinated pesticides [dichlorodiphenyltrichloroethane (*p*,*p*′-DDT), trans-nonachlor, dichlorodiphenyldichloroethylene (*p*,*p*′-DDE), hexachlorobenzene (HCB), and oxychlor], but not with PCBs, were observed with metabolic syndrome, which includes components of elevated blood pressure (Rosenbaum et al. 2017).

We conducted a follow-up of the ACHS I study in 2014 (ACHS II) to build on the baseline study and evaluate selected incident health outcomes, as well as to assess associations with other chemicals. In addition to PCBs, ACHS II also included PCDDs, PCDFs, and non-*o*-PCBs (Birnbaum et al. 2016). In this current analysis, we evaluated the relationship between serum concentrations of PCBs and dioxin toxic equivalencies (TEQs) with hypertension prevalence and incidence of hypertension. We used structure–activity PCB groups such as estrogenic, anti-estrogenic, thyroid-like, and others (Warner et al. 2012; Consonni et al. 2012; Hansen 1998) to contrast aryl hydrocarbon receptor (AhR)–dependent mechanisms (Murray et al. 2014), as represented by dioxin TEQs with nondioxin-like PCBs, which operate through mechanisms independent of the AhR. We also studied whether those chemicals have any relationship with cytokine levels as biomarkers of systemic inflammation in those individuals with hypertension.

Methods

In 2014, ACHS II was conducted as a follow-up of the 2005–2007 ACHS I study of the residents of Anniston, Alabama. All surviving ACHS I participants were eligible for the study. Of the original 765 study subjects, 114 were confirmed dead from the Social Security Index, and 69 were confirmed by site visits and

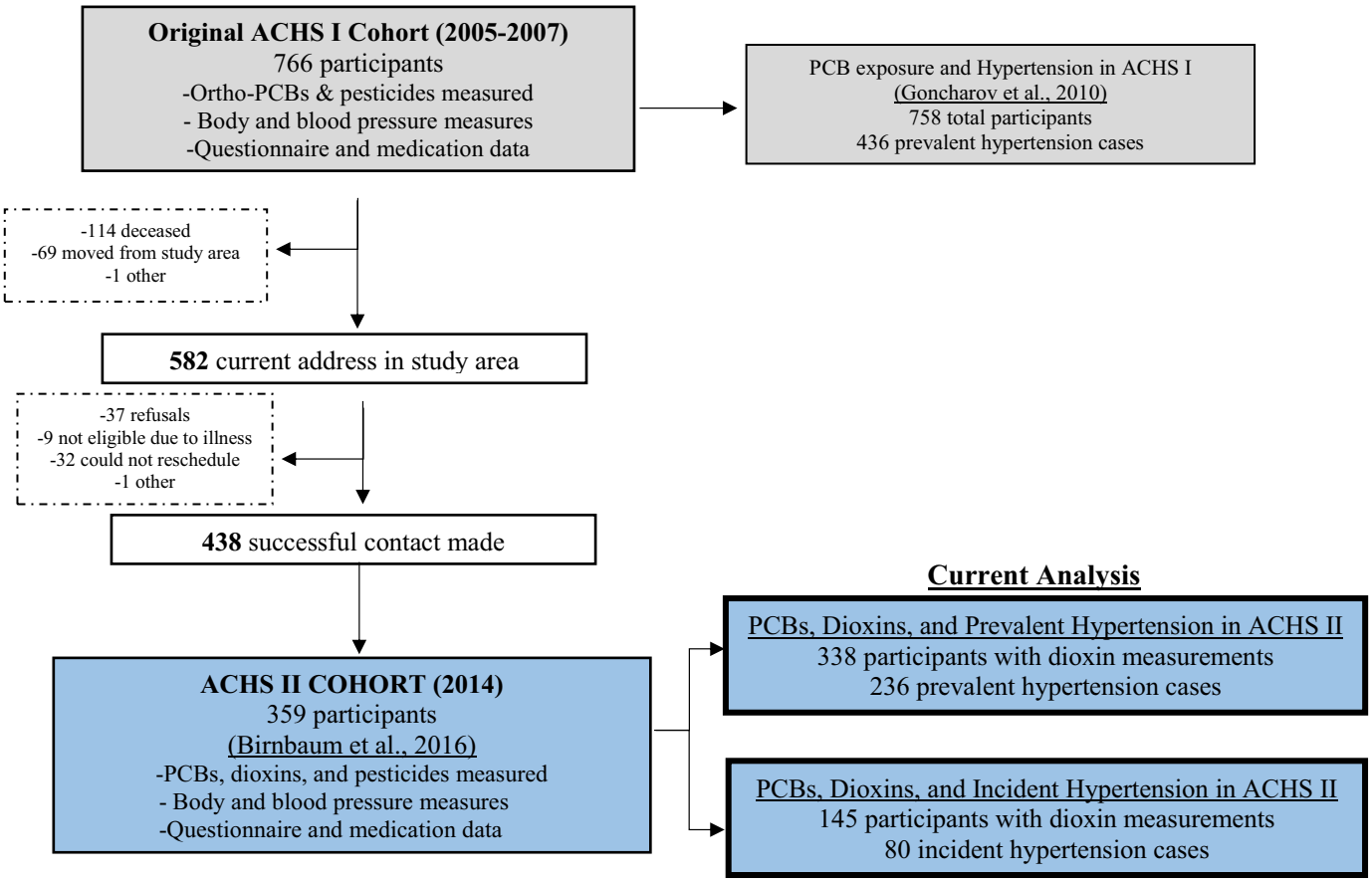

Figure 1. Overview of participant selection and data collection for the follow-up study Anniston Community Health Survey (ACHS II). TEQ, toxic equivalency.

phone calls by our staff to have moved out of the study area (Birnbaum et al. 2016). We successfully contacted 438 respondents, of whom 359 were enrolled in ACHS II (Figure 1). For the current analyses, each participant had his/her systolic and diastolic blood pressure measured three times manually by a certified nurse using a standard sphygmomanometer, arm cuff (three different sizes available), and stethoscope at 2-min intervals, beginning after the individual had been sitting for 5 min. Study office temperature was kept constant at 72°F, and light snacks and drinks were available to study participants. Participants were asked to bring in current prescription medications; those medications were used to determine whether the participant was on antihypertensive medication. The study nurse transcribed the drug name, dosage, and frequency. This information was used later to create variables of medication grouping by the University of Alabama Birmingham (UAB) research staff including 12 categories of hypertension/heart failure/angina medication (angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, combination, calcium channel blockers, nitrates, beta-blockers, alpha-/beta-blockers, alpha-blockers, central alpha-agonists, diuretics, aldosterone blockers, and vasodilators).

Hypertension, the primary outcome of interest, was defined as either taking antihypertensive medication or having an averaged second and third measured systolic blood pressure >140 mmHg and/or averaged diastolic pressure >90 mmHg (Krakoff et al. 2014). Hypertension self-reports were not used in this study. In-person interviews were conducted using questionnaires to assess participants' health and behaviors. Of 359 participants completing a questionnaire, 338 provided a sufficient fasting blood sample for chemical analyses. The study was reviewed, and approval was obtained from the Institutional Review Board at the Centers for Disease Control and Prevention (CDC).

Laboratory Analysis

The sera were isolated by centrifugation using red top vacutainer tubes and shipped on dry ice to the Division of Laboratory Sciences at the CDC, National Center for Environmental Health (NCEH). Participant samples were stored at −70°C.

Serum samples were first measured for PCDD/F and non-*o*-PCBs based on published methodology (Turner et al. 1997) using 20 g of serum (median: 20 g; range: 2.5−20.7 g; 10th percentile: 14.0 g). The samples were then measured for *o*-PCBs according to published methodology (Sjödin et al. 2004; Jones et al. 2012) using 2 g of serum. Each analytical batch for *o*-PCBs was defined as 24 unknowns, 3 quality controls, and 3 method blanks, while for PCDD/F and non-*o*-PCBs, each analytical batch included 8 unknowns, 2 quality controls, and 2 method blanks. Measurements of target organohalogens were made by gas chromatography–isotope dilution–high-resolution mass spectrometry.

Cytokines were measured using two separate multiplex bead arrays on a Luminex IS100 system (EMD Millipore Corporation) at the University of Louisville. The first array (HADK2MAG-61K) measured IL-1β and TNFα. For the measurement of IL-6, IL-8, and IL-17, the State University of New York Molecular Analysis Core laboratory used the MILLIPLEX® MAP Human High-Sensitivity T-Cell 21-Plex Panel (EMD Millipore catalog number HSTCMAG28SPMX21). All techniques were performed per the Millipore protocol using quality control reagents and standards provided with the kit (Milliplex Assay Guide). As listed in the panel documentation, standard curve ranges are IL-6 (0.18−750 pg/mL), IL-8 (0.31−1,250 pg/mL), and IL-17 (0.73−3,000 pg/mL). Additional details concerning the standard curves can be found in the application note by Keith et al. (2015).

Statistical Analysis

Descriptive measures and exposure variables. All statistical analyses were conducted using SAS (version 9.4; SAS Institute Inc.) and R (version 3.3.0; R Development Core Team) packages. Descriptive statistics were calculated for outcome variables, demographic characteristics, and exposure variables; differences were compared using a two-tailed *t*-test for continuous variables and chi-square tests for categorical variables. Analyses of individual PCB congeners were undertaken if more than 60% of the samples had values above the limits of detection. We also created several summary exposures variables. The sum of 35 PCBs was created by adding together the mass of all 35 congeners specified in Pavuk et al. (2014a). We also evaluated the potential associations of several PCB structure–activity groups as classified by Warner et al. (2012) and others as shown in Table 1. Dioxin categories are based on structure–activity groups, selected from the best-available literature for PCB groupings using the review from Warner et al. (2012) as a basis (Table 1).

In order to calculate total dioxin TEQ, PCDD, PCDF, non-*o*-PCB, and mono-*o*-PCB congeners were assigned a potency relative to 2,3,7,8-TCDD [TEQ factor (TEF) = 1]. We multiplied the TEF values by the associated congener concentration to attain specific TEQs (Van den Berg et al. 2006). PCDD TEQ, PCDF TEQ, non-*o*-PCB TEQ, and mono-*o*-PCB TEQ were the sum of the individual congener classifications. Total dioxin TEQ was the sum of the four dioxin-like compound group TEQs listed previously.

Hypertension prevalence analyses. We used unconditional logistic regression to model hypertension status with exposure variables including summary TEQs and summary PCB groups. Summary TEQs and PCB groups were analyzed both as wet weight (or whole weight, ng/g serum) and as lipid-adjusted variables (ng/g lipid). Each continuous exposure variable was $\log_{10}$ transformed (Bernert et al. 2007). The adjusted models included age (years), sex (female, male), race (African American, white), total lipids [(mg/dL) for wet weight models only], body mass index (BMI) (kg/m^2), family history of high blood pressure (yes, no), and smoking status (smoked at least 100 cigarettes in lifetime, never smoked). These variables are established risk factors for cardiovascular disease and were therefore deemed appropriate for inclusion in all adjusted models. We evaluated additional covariates as potential confounders in the adjusted models such as measures of physical activity, alcohol consumption (at least 12 drinks in lifetime), and education. These variables did not change the effect estimates by more than 10%, were not associated with hypertensive status, and, therefore, were not included in the final models.

Regression models for cytokines analyses. Adjusted multivariate linear regression models and analysis of covariance were used in the cytokine analyses. We restricted those models to individuals with hypertension, excluding all participants without it ($n = 263$). We used total dioxin TEQ and sum nondioxin-like PCBs as exposures in these analyses. As in the logistic regression models, exposure variables were log transformed and similar covariates included for confounder adjustment.

Linear regression modeling for predicting continuous blood pressure readings. In multivariate linear regression models of systolic and diastolic blood pressure, the individuals on antihypertensive medication were removed, leaving 124 participants available for analyses. Exposure variables included summary chemical groupings that were then log transformed. The covariates included for confounder adjustment were the same as those used in the logistic regression models and defined above.

Hypertension incidence analyses. For hypertension incidence analyses, incident cases were defined as not being hypertensive

Table 1. Groupings of PCB congeners and dioxin compounds used for analyses.

PCB structure–activity group	Congeners and compounds included	Source
Sum 35	28, 44, 49, 52, 66, 74, 87, 99, 101, 105, 110, 118, 128, 138 + 158, 146, 149, 151, 153, 156, 157, 167, 170, 172, 177, 178, 180, 183, 187, 189, 194, 195, 196 + 203, 199, 206, 209	Warner et al. 2012
Estrogen I	44, 49, 66, 74, 99, 110, 128	DeCastro et al. 2006; Silverstone et al. 2012
Estrogen II	52, 99, 101, 110, 153	Warner et al. 2012
Anti-estrogenic	66, 74, 105, 118, 156, 167	Warner et al. 2012; Cooke et al. 2001; Wolff et al. 1997; combined Wolff and Cooke groupings
Thyroid-like	28, 52, 74, 101, 105, 118	Hansen 1998
Ryanodine-like	52, 101, 149, 151, 170, 180, 183, 187	Pessah et al. 2006
Mono-*o*-substituted	28, 66, 74, 105, 118, 156, 157, 167, 189	Warner et al. 2012
Di-*o*-substituted	44, 49, 52, 87, 99, 101, 128, 138 + 158, 146, 153, 170, 172, 180, 194	Warner et al. 2012
Tri, tetra-*o*-substituted	149, 151, 177, 178, 183, 187, 195, 196 + 203, 199, 206	Warner et al. 2012
Dioxin categories		
PCDDs	2,3,7,8-TCDD; 1,2,7,8-PCDD; 1,2,3,4,7,8-HCDD; 1,2,3,6,7,8-HCDD; 1,2,3,7,8,9-HCDD; 1,2,3,4,6,7,8-HCDD; OCDD	Van den Berg et al. 2006
PCDFs	2,3,7,8-TCDF; 1,2,3,7,8-PCDF; 2,3,4,7,8-PCDF; 1,2,3,4,7,8-HCDF; 1,2,3,6,7,8-HCDF; 1,2,3,7,8,9-HCDF; 2,3,4,6,7,8-HCDF; 1,2,3,4,6,7,8-HCDF; 1,2,3,4,7,8,9-HCDF; OCDF	Van den Berg et al. 2006
Mono-*o*-PCBs	105, 118, 156, 167, 189, 114, 123	Van den Berg et al. 2006
Non-*o*-PCBs	81, 126, 169	Van den Berg et al. 2006
Total dioxins	All above	Van den Berg et al. 2006

Note: HCDD, hexachlorodibenzo-*p*-dioxin; HCDF, hexachlorodibenzofuran; *o*, ortho; OCDD, octachlorodibenzodioxin; OCDF, octachlorodibenzofuran; PCB, polychlorinated biphenyl; PCDD, polychlorinated dibenzo-*p*-dioxin; PCDF, polychlorinated dibenzofuran; TCDD, tetrachlorodibenzodioxin.

in ACHS I and then developing hypertension in ACHS II; those who were hypertensive in ACHS I were censored/categorized as missing in the follow-up phase. There were 80 incident cases out of 145 nonhypertensive participants eligible for incidence analyses. We used logistic regression and proportional hazard regression to analyze the likelihood of becoming an incident hypertension case among all participants not meeting the criteria for hypertension in ACHS I. The time component for proportional hazard regression was created using all available information from questionnaire and medication data. The baseline time was the age of the participant at the ACHS I blood draw date. Twenty-one participants reported age at high blood pressure diagnoses, which we used to subtract the age at baseline. We substituted age of diagnosis for hypertension for age of diagnosis for other heart disease (stroke, heart attack, congestive heart failure, or coronary heart disease) for 11 participants who did not report a hypertension date of diagnosis. The remaining 48 incident hypertension cases were diagnosed at the follow-up clinic examination taking antihypertensive medication ($n = 17$) or measured high blood pressure ($n = 31$). The time component for the nonhypertensive participants was attained by subtracting the ACHS I blood draw date from the ACHS II interview date/blood draw date. Among the incident hypertensive cases, 49 (61.3%) were taking antihypertensive medication; these participants had 291.9 total person-years since ACHS I. The remaining 31 incident cases had elevated averaged systolic and/or diastolic blood pressure levels, with 213.3 total person-years. The 65 nonhypertensive participants had 496.4 total person-years since ACHS I.

In addition to PCB summary groups, we analyzed incident hypertension with estimated ACHS I TEQs. Concentrations of PCDD, PCDF, mono-*o*-, and non-*o*-PCB TEQs for ACHS I were calculated using linear regression modeling based on a pilot dioxin exposure study ($n = 65$) in 2007 (Pavuk et al. 2014b). The beta coefficients and intercepts were used to estimate the missing ACHS I values for all ACHS II participants not included in the pilot study ($n = 303$); ACHS I TEQs were the outcomes, and ACHS II TEQs were the sole predictors in these models. Thirty-five of the pilot study participants took part in both ACHS I and the follow-up ACHS II and provided validation of the estimated concentrations (Yang et al. 2018).

Results

Demographic characteristics of the study population are presented in Table 2. The majority of participants were classified as hypertensive (77.8%), of whom 214 (81.4%) were on antihypertensive medication; 49 (18.6%) were classified as having hypertension at the study visit based on elevated diastolic and or systolic levels. The mean age for participants with and without hypertension was 64.3 and 56.9 y respectively; all participants self-identified as either African-American (55.9%) or white. The means of several health demographics were similar for the hypertension and nonhypertension groups: total lipid (623.7 mg/dL and 620.0 mg/dL, respectively). BMI was higher in individuals with hypertension (32.0 kg/m^2) than in individuals without hypertension (30.5 kg/m^2). In both groups, the study participants were predominantly female and nonsmokers. Overall, those who had hypertension were older and were more likely to be African-American than white. Across exposures, participants with hypertension had higher concentrations of total dioxins and nearly three times greater exposure to PCBs; correlations between these groups are presented in Figure 2. There was a high correlation between PCB groups, with weaker correlations seen between PCBs and *p*,*p*′-DDE and dioxins.

Table 3 presents odds ratios (ORs) of hypertension with $\log_{10}$-transformed dioxin TEQs. TEQ variables were modeled as wet weight with total lipids as a covariate in both the unadjusted and adjusted models (lipid-normalized results shown in Table S1). Total dioxin TEQ was only modestly elevated {1.63 [95% confidence interval (CI): 0.53, 4.99]}, similar to adjusted odds of hypertension seen for PCDD TEQ and PCDF TEQ. Stronger increases were seen for mono-*o*-PCB TEQ [2.08 (95% CI: 0.91, 4.77)] and non-*o*-PCB TEQ [1.99 (95% CI: 0.93, 4.23)]. When dioxin-like PCB groups were divided into quartiles, non-*o*-PCBs showed a monotonic trend in the adjusted model [Q2: 1.81 (95% CI: 0.87, 3.79), Q3: 2.43 (95% CI: 1.09, 5.44), and Q4: 3.66 (95% CI: 1.40, 9.56)] and quartiles 3 and 4 were statistically significant (Table 4). Mono-*o*-PCB also showed positive ORs in an adjusted model assessing hypertension but to a lesser degree [Q2: 1.34 (95% CI: 0.60, 3.02), Q3: 2.13 (95% CI: 0.86, 5.30), and Q4: 1.59 (95% CI: 0.53, 4.71)]. A comparison of these estimates to quartiles of lipid-adjusted substituted TEQs (Table S2) demonstrated a similar magnitude and direction of effect, but the whole-weight analysis was stronger.

Table 2. Demographics and exposures of ACHS II participants stratified by hypertension status at follow-up in 2014.

Demographics	Hypertension ($n = 263$)	Nonhypertension ($n = 75$)	p-Value
Age (y)	64.3 ± 11.8	56.9 ± 15.3	0.0002
BMI (kg/m^2)	32.0 ± 8.2	30.5 ± 7.8	0.17
African Americans	147 (55.9%)	25 (33.3%)	0.0006
Females	193 (73.4%)	52 (69.3%)	0.49
Total lipid (mg/dL)	623.7 ± 159.3	620.0 ± 140.0	0.86
Triglycerides (mg/dL)	135.9 ± 91.0	118.7 ± 73.6	0.1335
Glucose	107.6 ± 57.5	88.6 ± 26.9	0.0057
Exercise in past month	94 (35.7%)	35 (46.7%)	0.0341
Education (>high school)	87 (33.3%)	32 (42.7%)	0.1363
Alcohol (lifetime)[a]	178 (67.7%)	52 (69.3%)	0.7866
Smoking status (lifetime)[b]	56 (21.3%)	15 (20.0%)	0.81
Family history of high blood pressure	208 (79.1%)	53 (70.7%)	0.13
Exposures			
Total TEQ (pg/g)	166.7 ± 151.5	99.3 ± 86.7	0.0003
Sum PCBs (pg/g)	6,433.8 ± 8,092.9	2,888.1 ± 3,257.0	0.0002
Sum nondioxin-like PCBs (pg/g)	5,423.4 ± 6,889.5	2,433.6 ± 2,706.3	0.0003
Total TEQ (pg/g lipid)	42.4 ± 112.8	27.0 ± 24.3	0.2425
Sum PCBs (ng/g lipid)	1,064.6 ± 1,248.3	511.6 ± 629.5	0.0003
Sum nondioxin-like PCBs (ng/g lipid)	895.6 ± 1,052.2	430.1 ± 520.2	0.0003

Note: Continuous variables presented as [mean ± standard deviation (SD)], categorical variables as n (%). ACHS II, Anniston Community Health Survey follow-up; BMI, body mass index; PCB, polychlorinated biphenyl; TEQ, toxic equivalency. p-Value for continuous variables determined by two-tailed t-test, $\alpha < 0.05$. p-Value for categorical variables determined by chi-square test, $\alpha < 0.05$.
[a]Alcohol status defined as having had at least 12 alcoholic drinks in lifetime/never drank.
[b]Smoking status defined as having smoked at least 100 cigarettes in lifetime/never smoked cigarette.

The adjusted ORs were increased for all nondioxin-like structure–activity PCB groups in ACHS II and also for the dioxin-like mono-*o*-congener group (Table 3); the strongest associations with hypertension were observed for the estrogenic I [2.36 (95% CI: 1.07, 5.22)], estrogenic II [2.54 (95% CI: 1.13, 5.74)], and thyroid-like PCB groups [2.25 (95% CI: 1.07, 4.75)], followed by the mono-*o*-PCBs [2.26 (95% CI: 0.97, 5.29)]. All ORs were at or above 1.78. Corresponding analyses for lipid adjusted PCB groups can be seen in Table S1.

As shown in Table 5, analyses of 26 individual PCB congeners strongly support the PCB group analyses. Fifteen of 26 congeners had ORs above 2.00, and an additional 6 were above 1.50. Strong positive associations were reported for the dioxin-like, mono-*o*-substituted, and potentially antiestrogenic congeners such

	PCDD TEQ										
PCDD TEQ	1	**Non-Ortho PCB TEQ**									
Non-ortho PCB TEQ	0.42 (<0.0001)	1	**Total Dioxin TEQ**								
Total Dioxin TEQ	0.71 (<0.0001)	0.93 (<0.0001)	1	**p,p'-DDE**							
p,p'-DDE	0.53 (<0.0001)	0.45 (<0.0001)	0.55 (<0.0001)	1	**Mono-ortho PCB**						
Mono-ortho PCB	0.47 (<0.0001)	0.91 (<0.0001)	0.91 (<0.0001)	0.47 (<0.0001)	1	**Di-ortho PCB**					
Di-ortho PCB	0.44 (<0.0001)	0.80 (<0.0001)	0.83 (<0.0001)	0.40 (<0.0001)	0.93 (<0.0001)	1	**Tri, tetra-ortho PCB**				
Tri, tetra-ortho PCB	0.38 (<0.0001)	0.64 (<0.0001)	0.68 (<0.0001)	0.30 (<0.0001)	0.75 (<0.0001)	0.90 (<0.0001)	1	**Estrogen I PCB**			
Estrogen I PCB	0.45 (<0.0001)	0.84 (<0.0001)	0.85 (<0.0001)	0.49 (<0.0001)	0.94 (<0.0001)	0.90 (<0.0001)	0.69 (<0.0001)	1	**Anti- estrogenic PCB**		
Anti-estrogenic PCB	0.46 (<0.0001)	0.90 (<0.0001)	0.90 (<0.0001)	0.46 (<0.0001)	1.00 (<0.0001)	0.93 (<0.0001)	0.76 (<0.0001)	0.93 (<0.0001)	1	**Thyroid- like PCB**	
Thyroid-like PCB	0.45 (<0.0001)	0.91 (<0.0001)	0.90 (<0.0001)	0.46 (<0.0001)	0.99 (<0.0001)	0.88 (<0.0001)	0.67 (<0.0001)	0.95 (<0.0001)	0.98 (<0.0001)	1	**Ryanodine-like PCB**
Ryanodine-like PCB	0.41 (<0.0001)	0.77 (<0.0001)	0.79 (<0.0001)	0.47 (<0.0001)	0.89 (<0.0001)	0.98 (<0.0001)	0.91 (<0.0001)	0.85 (<0.0001)	0.88 (<0.0001)	0.83 (<0.0001)	1

Figure 2. Pearson correlation matrix between whole weight structure–activity polychlorobiphenyl (PCB) groups, selected dioxin categories, and dichlorodiphenyldichloroethylene (p,p'-DDE).

Table 3. Logistic regression models of dioxin TEQs, PCB groups (whole weight), and hypertension.

TEQ (pg/g)	*n* (hypertension/total)	Adjusted OR (95% CI)
PCDD	262/337	1.67 (0.43, 6.40)
PCDF	261/336	1.88 (0.49, 7.25)
Mono-*o*-PCB	263/338	2.08 (0.91, 4.77)
Non-*o*-PCB	251/313	1.99 (0.93, 4.23)
Total dioxin	263/338	1.63 (0.53, 4.99)
PCB groups		
Sum	263/338	2.27 (0.92, 5.61)
Mono-*o*	263/338	2.26 (0.97, 5.29)
Di-*o*	263/338	1.91 (0.78, 4.70)
Tri, tetra-*o*	263/338	1.78 (0.76, 4.20)
Estrogenic I	263/338	2.36 (1.07, 5.22)
Estrogenic II	263/338	2.54 (1.13, 5.74)
Anti-estrogenic	263/338	2.08 (0.91, 4.77)
Thyroid-like	263/338	2.25 (1.07, 4.75)
Ryanodine	263/338	2.17 (0.88, 5.38)

Note: Adjusted models include $\log_{10}$-transformed total lipids, age, sex, race, body mass index (BMI), smoking status, and family history of high blood pressure. CI, confidence interval; *o*, ortho; OR, odds ratio; PCB, polychlorinated biphenyl; PCDD, polychlorinated dibenzo-*p*-dioxin; PCDF, polychlorinated dibenzofuran; TEQ, toxic equivalency.

as congeners 74, 99, 105, 118, and 167. The nondioxin like, di-*o*-congeners 138 and 153, as well as the tri- and tetra-*o*-, ryanodine-like congeners 177, 183, and 187 also showed strong positive associations with hypertension status; these 5 ORs were between 2 and 3, with CIs not including 1.

We also analyzed the linear relationship between chemical groups, both as TEQs and PCB subsets, and measures of systolic and diastolic blood pressure obtained during the follow-up study office visit for participants not taking antihypertensive medication (Table S3 and Figures S1 and S2). Overall, no strong links between PCB concentrations or TEQs and blood pressure measurements were observed, although some weak associations were found for systolic blood pressure.

Table 4. Logistic regression models of summary $\log_{10}$ dioxin TEQ quartiles (pg/g whole weight) and hypertension.

Dioxin TEQ group (cut point)	*n* (hypertension/total)	Adjusted OR (95% CI)
PCDD TEQ	262/337	—
Q1 (<1.578)	55/85	1.0 (referent)
Q2 (1.578–1.774)	64/83	1.39 (0.63, 3.06)
Q3 (1.774–1.920)	71/84	1.65 (0.64, 4.27)
Q4 (≥1.920)	72/85	1.11 (0.38, 3.21)
PCDF TEQ	261/336	—
Q1 (<0.91)	61/84	1.0 (referent)
Q2 (0.981–1.146)	65/84	0.98 (0.44, 2.17)
Q3 (1.146–1.295)	61/84	0.66 (0.28, 1.52)
Q4 (≥1.295)	74/84	1.12 (0.41, 3.06)
Mono-*o*-PCB TEQ	263/338	—
Q1 (<0.628)	49/84	1.0 (referent)
Q2 (0.628–0.926)	67/85	1.34 (0.60, 3.02)
Q3 (0.926–1.319)	73/85	2.13 (0.86, 5.30)
Q4 (≥1.319)	74/84	1.59 (0.53, 4.71)
Non-*o*-PCB TEQ	263/338	—
Q1 (<1.064)	64/104	1.0 (referent)
Q2 (1.064–1.337)	62/78	1.81 (0.87, 3.79)
Q3 (1.337–1.730)	66/78	2.43 (1.09, 5.44)
Q4 (≥1.730)	71/78	3.66 (1.40, 9.56)
Total dioxin TEQ	263/338	—
Q1 (<1.794)	57/85	1.0 (referent)
Q2 (1.794–2.029)	58/84	0.68 (0.32, 1.46)
Q3 (2.029–2.245)	72/85	1.52 (0.60, 3.82)
Q4 (≥2.245)	76/84	1.43 (0.45, 4.50)

Note: —, no data; CI, confidence interval; *o*, ortho; OR, odds ratio; PCB, polychlorinated biphenyl; PCDD, polychlorinated dibenzo-*p*-dioxin; PCDF, polychlorinated dibenzofuran; Q, quartile; TEQ, toxic equivalency.

Table 5. Logistic regression models of individual ortho-substituted PCB congeners (ng/g whole weight) and hypertension.

PCB congeners (ng/g)	*n*[a]	Adjusted OR (95% CI)
28	205/253	1.44 (0.54, 3.83)
66	197/233	0.82 (0.30, 2.25)
74	262/335	2.76 (1.14, 6.73)
99	262/336	2.18 (1.10, 4.33)
105	252/316	2.00 (0.95, 4.22)
114	233/283	2.72 (0.90, 8.25)
118	263/338	2.02 (1.00, 4.07)
138	261/335	2.70 (1.21, 6.04)
146	263/336	2.11 (0.97, 4.62)
153	263/338	2.57 (1.13, 5.86)
156	262/335	1.68 (0.67, 4.21)
157	255/318	1.89 (0.70, 5.09)
167	257/322	2.37 (1.03, 5.47)
170	263/337	1.97 (0.78, 5.02)
172	219/280	2.70 (0.96, 7.54)
177	259/322	2.49 (1.09, 5.70)
178	260/330	1.80 (0.77, 4.19)
180	262/337	2.05 (0.80, 5.25)
183	262/332	2.47 (1.11, 5.45)
187	262/336	2.41 (1.08, 5.40)
189	237/293	2.17 (0.65, 7.22)
194	262/335	1.36 (0.55, 3.38)
195	254/316	2.67 (0.95, 7.49)
196	263/337	1.91 (0.76, 4.83)
199	262/336	1.48 (0.63, 3.47)
206	262/334	0.98 (0.44, 2.17)
209	257/327	0.93 (0.46, 1.89)

Note: Adjusted models include $\log_{10}$-transformed lipids, age, sex, race, body mass index (BMI), smoking status, and family history of high blood pressure. PCB congeners shown have >60% limit of detection (LOD). CI, confidence interval; OR, odds ratio; PCB, polychlorinated biphenyl.
[a]Number of individuals with hypertension/total.

In the analyses of incident hypertension, we detected 80 new cases from the baseline in 2005–2007 to the follow-up in 2014, with a total of 505.2 person-years. As shown in Table 6, incident cases were, on average, 5 y older than those without hypertension and were more likely to be African-American and have higher serum levels of sum PCBs, sum of nondioxin-like PCBs, and total TEQs. The proportional hazard ratios (HRs) for the dioxin-like TEQs ranged from 1.33 to 2.16 and from 1.48 to 1.93 for the PCB-structure–activity groups; all CIs included the value 1 (Table 7). The strongest associations were observed for estrogenic II PCBs [1.90 (95% CI: 0.96, 3.78)], the di-*o*-PCBs [1.93 (95% CI: 0.93, 4.00)], and the sum of all PCBs congeners [1.89 (95% CI: 0.91, 3.90)]. While the reported CIs include 1, the data are supportive of an increased risk of hypertension rather than no association; this is especially apparent for the PCB groups (Table 7).

Incidence analyses using TEQ tertiles as the exposure variables revealed a nonmonotonic pattern of increases in the second tertile but a similar or lower HR in the third tertile. The strongest association was found between the second tertile of mono-*o*-PCB TEQ and hypertension [HR = 2.00 (95% CI: 1.11, 3.62)] (Table S4).

Geometric means for several inflammatory cytokines (TNFα, IL-1β, IL-6, IL-8, and IL-17) reported to be involved in the development of hypertension were higher in hypertensive subjects in ACHS II than in those without hypertension for all studied cytokines; the biggest differences were observed for IL-6, IL-8, and IL-17, but none of these reached statistical significance (Table 8). These geometric means were adjusted for age, sex, race, gender, and BMI. We also wanted to know whether increases in cytokine concentrations, as biomarkers of systemic inflammation, were in some way related to increases in dioxin TEQ or PCB exposures. We contrasted dioxin TEQs

Table 6. Demographics of participants included in incident analyses: ACHS I participants without hypertension stratified by their hypertension status in ACHS II.

Demographics	Hypertensive ($n = 80$)	Nonhypertensive ($n = 65$)	p-Value
Age (y)	59.84 ± 1.5	54.34 ± 1.9	0.048
BMI (kg/m^2)	30.60 ± 0.8	30.16 ± 0.9	0.73
African Americans	44 (55%)	24 (36.9%)	0.03
Females	55 (68.8%)	48 (73.8%)	0.50
Total lipids (mg/dL)	677.02 ± 22.2	629.86 ± 17.9	0.11
Triglycerides	153.43 ± 13.7	119.14 ± 9.5	0.052
Glucose	107.03 ± 7.6	85.88 ± 2.7	0.017
Exercise in past week	52 (65%)	44 (67.7%)	0.8600
Education >high school	28 (35%)	32 (49.2%)	0.0925
Alcohol (past month)[a]	30 (37.5%)	17 (36.2%)	0.1582
Smoking status (lifetime)[b]	21 (26.3%)	13 (20%)	0.38
Family history of high blood pressure (yes)	68 (85%)	45 (69.2%)	0.023
Exposures			
Total TEQ (pg/g)	145.15 ± 16.1	91.41 ± 9.5	0.008
Sum PCBs (pg/g)	5,930.46 ± 974.3	2,868.70 ± 417.7	0.0084
Sum nondioxin-like PCBs (pg/g)	6,034.11 ± 893.95	3,325.05 ± 412.22	0.013
Total TEQ (pg/g lipid)	54.1 ± 22.5	25.4 ± 2.9	0.2548
Sum PCBs (ng/g lipid)	858.4 ± 118.9	496.6 ± 78.6	0.0170
Sum nondioxin-Like PCBs (ng/g lipid)	838.5 ± 115.5	482.0 ± 76.3	0.0155

Note: Continuous variables presented as [mean ± standard deviation (SD)]; categorical variables presented as n (%). ACHS, Anniston Community Health Survey; BMI, body mass index; PCB, polychlorinated biphenyl; TEQ, toxic equivalency. p-Value for continuous variables determined by two-tailed t-test, $\alpha < 0.05$. p-Value for categorical variables determined by chi-square test, $\alpha < 0.05$.
[a]Alcohol status defined as having had at least one alcoholic drink in the past 30 days/never drank.
[b]Smoking status defined as having smoked at least 100 cigarettes in lifetime/never smoked cigarettes.

and the sum of nondioxin-like PCBs with the concentrations of inflammatory cytokines among participants with hypertension in ACHS II (Table S5). Higher-dioxin TEQs were related to higher inflammatory cytokines levels, but the associations were weak and did not reach statistical significance. The nondioxin-like PCBs showed inverse associations with all inflammatory cytokines studied except IL-1β. Linear regression of cytokine values for participants without hypertension can be seen in Table S6.

Discussion

With the follow-up to ACHS I, we conducted a longitudinal study 8 y after the baseline to investigate the relationship between persistent chlorinated compounds and hypertension in this older, predominantly female, and biracial cohort of residents living around the former PCB production plant in Anniston, Alabama. We observed positive associations with prevalent hypertension for a number of individual PCB congeners and both nondioxin-like PCB structure–activity groups, as well as dioxin-like compounds modeled as TEQs. The strongest (and statistically significant) adjusted ORs were reported for PCBs 74, 99, 138, 153, 167, 177, 183, and 187 [ORs ranging from 2.18 (95% CI: 1.10, 4.33) to 2.76 (95% CI: 1.14, 6.73)], two estrogenic-like PCB groups, and the thyroid-like group [ORs ranging from 2.25 (95% CI: 1.07, 4.75) to 2.54 (95% CI: 1.13, 5.74)]. Furthermore, analysis of quartiles demonstrated a monotonic relationship for dioxin-like non-*o*-PCB TEQs [fourth vs. first quartile: 3.66 (95% CI: 1.40, 9.56)]. Longitudinal analyses of incident hypertension supported those positive associations. The results were strongest for the di-*o*-PCBs [1.93 (95% CI: 0.93, 4.00)] and estrogenic II PCB group [1.90 (95% CI: 0.96, 3.78)] but were weaker for the dioxin TEQs. Overall, these data are supportive of associations of PCBs with both prevalent and incident hypertension, despite not always meeting the requirements of statistical significance (Amrhein et al. 2019; Rothman et al. 2008).

Table 7. Proportional hazard models of dioxin TEQs, PCB groups (pg/g whole weight), and hypertension; longitudinal assessment.

TEQs (pg/g)	n^a	Adjusted HR (95% CI)
PCDD	79/144	2.16 (0.36, 12.94)
PCDF	78/143	1.81 (0.33, 10.02)
Mono-*o*-PCB	80/145	1.70 (0.89, 3.25)
Non-*o*-PCB	73/125	1.33 (0.78, 2.28)
Total dioxin	80/145	1.47 (0.54, 3.96)
PCB groups		
Sum	80/145	1.89 (0.91, 3.90)
Mono-*o*	80/145	1.70 (0.86, 3.38)
Di-*o*	80/145	1.93 (0.93, 4.00)
Tri, tetra-*o*	80/145	1.81 (0.93, 3.56)
Estrogenic I	80/145	1.60 (0.83, 3.07)
Estrogenic II	80/145	1.90 (0.96, 3.78)
Anti-estrogenic	80/145	1.70 (0.89, 3.25)
Thyroid-like	80/145	1.48 (0.81, 2.70)

Note: Adjusted for $\log_{10}$-transformed total lipids, age, body mass index (BMI), race, sex, and family history of high blood pressure. TEQs imputed (Yang et al. 2018). CI, confidence interval; HR, hazard ratio; PCB, polychlorinated biphenyl; PCDD, polychlorinated dibenzo-*p*-dioxin; PCDF, polychlorinated dibenzofuran; TEQ, toxic equivalency.
[a]Number of individuals with hypertension/total.

Evidence from Longitudinal Studies

Results from the Anniston cohort built on the data from four other cohort studies that examined possible associations between POPs and hypertension and were conducted in Sweden, Spain, and Italy. In a Swedish cohort study with a 10-y follow-up, Donat-Vargas et al. (2018) found positive associations between hypertension and dioxin-like PCBs (sum of mono-*o*-PCBs 118 and 156) in 1,511 middle-aged men and women. The multivariable-adjusted OR of hypertension based on repeated measurements was 1.52 (95% CI: 1.08, 2.13) for the dioxin-like PCBs, which was similar in direction and magnitude to the HR for our mono-*o*-PCBs group [1.70 (95% CI: 0.86, 3.38)]; our sample size in the incidence analyses was considerably smaller ($n = 145$). We also reported increased ORs for these congener groups in our prevalence analyses, and they were significantly higher (2.70 and 2.57, respectively). In contrast, Donat-Vargas did not observe a strong association for nondioxin-like PCBs analyzed as a group (sum of PCBs 74, 99, 138, 153, 170, 180, 183, and 187).

Table 8. Geometric means of inflammatory cytokines in ACHS I and ACHS II.

	ACHS I			ACHS II		
Cytokines	Hypertension	No hypertension	p-Value[a]	Hypertension	No hypertension	p-Value[a]
TNFα	2.93	3.07	0.42	3.02	2.94	0.71
IL-1β	0.39	0.44	0.32	0.35	0.30	0.31
IL-6	0.46	0.46	0.90	0.50	0.40	0.07
IL-8	10.50	10.15	0.86	4.43	3.99	0.44
IL-17	2.42	3.04	0.06	2.60	2.47	0.70

Note: Reference levels of tumor necrosis factor-α (TNFα), interleukin 1β (IL-1β), and interleukin 6 (IL-6) for persons 70 years of age or older in the Framingham Heart Study were reported as 1.30 ± 0.81 for TNFα, 1.12 ± 0.95 for IL-1β, and 1.15 ± 0.89 for IL-6 (Roubenoff et al. 2003). ACHS, Anniston Community Health Survey.
[a]$\alpha < 0.05$.

A study of similar size and length of follow-up to Anniston was conducted by Arrebola et al. (2015). Two hundred ninety-seven residents in Granada, Spain, were recruited between 2003 and 2004 and followed for 10 y. Positive associations between several POPs and hypertension incidence were reported, especially in those with a BMI above 26 kg/m^2. The HRs in their study ranged from 1.20 to 1.36 and were statistically significant for PCBs 138, 153, the sum of PCBs, and two pesticides: HCB, and β-hexachlorocyclohexane. HRs of similar magnitude and borderline statistical significance were noted for PCB 180 and p, p'-DDE as well. The magnitude of increase in HRs with the nondioxin-like PCB congeners is similar to the results of the present longitudinal study in Anniston. The median concentrations of selected PCB congeners in this Granada cohort (samples collected in 2003–2004) were higher than in Anniston at baseline in 2005–2007; PCB 138 was 74 vs. 123 ng/g lipid; PCB 153 was 203 vs. 176 ng/g lipid. The Granada cohort was of similar age as the ACHS II participants included in the incidence analyses (median ages of 48 and 50 y in Spain and Anniston, respectively). However, the Spanish cohort's BMI indicated that the population was only overweight (median BMI: 26.3 kg/m^2), while ACHS II participants were obese on average (median BMI: 30.5 kg/m^2).

A prospective study in Brescia, Italy, enrolled residents from the industrial area similar to Anniston surrounding the chemical factory where PCBs were produced from 1938 to 1984, with contamination found in local soil and food (Raffetti et al. 2018). A dose–response relationship was observed between serum levels from the sum of 24 PCB congeners and the onset of hypertension; the adjusted relative risks for the second and third tertiles of the serum PCB distribution were 2.07 (95% CI: 1.18, 3.63) and 2.41 (95% CI: 1.30, 4.47), respectively, in 1,331 participants. Although the measured PCBs differ between studies to some extent, our longitudinal analysis of the sum of 35 PCB congeners resulted in a similarly elevated HR for hypertension [HR = 1.89 (95% CI: 0.91, 3.90)].

A fourth large follow-up study also was conducted in Spain with 1,497 cases of hypertension among 14,521 participants; the median follow-up was 8.3 y (Donat-Vargas et al. 2015). PCB concentrations were not measured. Instead, the PCB intake was estimated based on validated food consumption questionnaires and measured PCB concentrations in food (Fernández-Ballart et al. 2010; Llobet et al. 2008). In agreement with other cohort studies, the investigators found a significant association between PCBs and hypertension incidence. Those in the fifth quintile of total PCB intake had a higher risk of developing hypertension [HR = 1.43 (95% CI: 1.09, 1.88)] than those in the first quintile.

Overall, the data from recent cohort studies provides growing support for the role of nondioxin-like PCB congeners, (e.g., 138, 153, and 180), as well as the dioxin-like mono-o-congeners (e.g., 118, 105, and 126) in the development of hypertension (reviewed by Park et al. 2016). However, most cohort studies and cross-sectional studies did not measure more than a few mono-o congeners and did not use analytical methods to support the analysis of more potent (AhR binding) dioxin-like non-o-PCB congeners. Our findings for the non-o-PCB congeners (126 and 169) provide the strongest support yet for the experimental/mechanistic findings.

Evidence from NHANES and Other Cross-Sectional Studies

The results of the cohort studies are supported by the results from a number of cross-sectional studies that examined serum PCB concentrations and hypertension. These studies have included exposures in the general U.S. population [e.g., National Health and Nutrition Examination Survey (NHANES)] as well as some high PCB–exposed cohorts. In cross-sectional analyses of NHANES data from 1999–2002, Everett et al. (2008) reported an increased risk of hypertension with higher serum concentrations of PCB congeners 138, 126, and 118; these findings mirror the strong associations noted with congeners 138 and 118 (Table 5) and with the non-o-PCB TEQ (sum of PCBs 126 and 169) and hypertension status in our study. Ha et al. (2009) reported a positive nonsignificant trend towards a greater hypertension risk with increasing concentrations of nondioxin-like o-substituted PCBs (138, 153, and 180) in separate analyses of the same NHANES data set (1999–2002). Inuit adults from Nunavik, Canada, who are highly PCB exposed due to local fish consumption were found to have congener levels about three times higher than those seen in Anniston (PCB 153 geometric mean of 1.71 μg/L vs. 0.568 μg/L in Anniston). Valera et al. (2013) found elevated hypertension ORs for lipid-adjusted mono-o-substituted PCB 105 and for the non-dioxin like di-o-PCBs 138 and 183.

Blood Pressure Results

Blood pressure analysis results using linear regression models demonstrated only weak positive associations with systolic and no association with diastolic blood pressure in this follow-up Anniston study. This contrasts with our earlier results in the ACHS I study for PCB congeners/groups and blood pressure (Goncharov et al. 2011) and the findings reported by Peters et al. (2014) for systolic pressure. The ACHS II findings for blood pressure are more in line with the null associations found in the Henríquez-Hernández et al. (2014) or Kreiss et al. (1981) papers, providing little support for a definitive association between PCBs or dioxin-like compounds and blood pressure.

Cytokines and Hypertension

We observed a marginally higher concentration of inflammatory cytokines in hypertensive subjects in this follow-up study, but there was little, if any, association with dioxin TEQ and PCBs. Recent mechanistic studies are suggestive of the importance of these biomarkers of inflammation in hypertension development (Norlander and Madhur 2017; Norlander et al. 2018; McMaster et al. 2015). The clinical trial of Canakinumab targeting IL-1β as a cytokine-based therapy (which also directly

stimulates the IL-6 receptor pathway) reported significantly lower mortality in those on inflammation-reducing therapy (Ridker et al. 2017). It is thus reasonable to investigate the potential role of PCBs and dioxin-like compounds as immune modulators in this setting. More extensive analyses will be required to disentangle the role of PCB congeners or dioxin-like compounds in these complex processes.

Strengths and Limitations

The ACHS II follow-up study in Anniston residents is one of the few prospective investigations of the relationship between POPs and hypertension. An additional strength of the study is the extensive number of chemicals analyzed, including 35 PCB congeners, dioxin-like compounds such as non-*o*-PCBs, as well as 2,3,7,8-substituted dioxins and furans. This analysis used previously reported PCB structure–activity groups (Table 1), which were created on the properties of specific congeners. While correlations between these groups are high in general (>0.80), lower correlations are seen for some groups such as thyroid-like and anti-estrogenic PCBs, which enables a better discrimination of results. Furthermore, all the structure-activity PCB groups showed weak correlations with *p*,*p*′-DDE and the dioxin TEQs (Figure 2). In addition, serum lipids have been shown to achieve good equilibrium with adipose tissue (Patterson et al. 1987, 2009); we included serum lipid concentration measurements before hypertension developed in our incidence analyses.

Furthermore, an adjustment was made for a number of well-known risk factors for hypertension, including a positive family history. Nurse-verified medication and direct measurement of blood pressure by study staff, as opposed to using self-report of hypertension, was undertaken as part of data collection, particularly since medical record review was not feasible in this community-based study. Participants were asked to bring medication into the study office, which was recorded on-site. Weight and height were also measured by study personnel at the baseline and follow-up examinations. The average change in BMI among the 338 participants was −0.28, which indicates that a few participants lost weight over the 8-y time period; hypertension development seemed to be independent of BMI or weight in our cohort.

Study limitations include a smaller sample size, as we could only enroll surviving members of the Anniston cohort who had not moved far (within a 1-h drive) from the study area. Nonetheless, the sample size was sufficiently large to identify a number of associations with good precision and narrow CIs such as those for the structure–activity PCB groups and individual congeners in the prevalence analyses. Statistical precision for the incidence analyses was more affected due to a high prevalence of hypertension in the original study. Individuals with hypertension recorded in ACHS I who participated in ACHS II were excluded from the incident hypertension follow-up assessment. Nevertheless, the hazard ratios observed and reported here were stronger than those noted in Arrebola et al. (2015), Donat-Vargas et al. (2018), or Raffetti et al. (2018). Those studies had 10 y of the follow-up on average vs. 8 y in the Anniston cohort. Longer follow-ups are desirable, but study results need to be relevant for the population sampled, and advanced age may further reduce the number of respondents in future follow-ups. Any aging cohort would have some loss to follow-up, and we have confirmed death status for 114 individuals through a National Death Index match based on name, date of birth, sex, race, and address. Of the 583 ACHS I participants who were alive and eligible to participate (last known addresses inside the study area), 438 were successfully contacted, and 359 individuals were enrolled in ACHS II (61.1% re-enrollment). Among the deceased from ACHS I ($n = 114$; Birnbaum et al. 2016), the OR for hypertension and sum of PCBs is 0.99 (95% CI: 0.27, 3.62) after adjusting for age, sex, and race, and this was unlikely to bias the observed associations seen in the participants of ACHS II. Continued follow-up of this population is unlikely, as close to 80% of the sample already has prevalent diagnosed hypertension; the number on antihypertensive medication increased from the first study from 75% to 81%. Also, per the American Heart Association guidelines, a second visit would be preferable for clinically based hypertension diagnosis. This was not feasible using this community-based design and also was not done in the other longitudinal cohorts discussed here that were not hospital based. The 78% prevalence of hypertension in the Anniston cohort is close to previously reported prevalence values in a population of ≥70-y-old men and women (72%) (Lind et al. 2014).

Conclusions

Our results add to the body of literature that examined the relationship between PCBs and other organochlorine compounds with hypertension in longitudinal epidemiological studies, especially for dioxin-like PCB congeners and dioxin TEQs not addressed elsewhere. We found associations with hypertension prevalence for PCB groups and dioxin TEQs, and these findings were further supported by our incidence analyses for PCBs. Additional research on biomarkers of exposure, inflammation, and hypertension may be needed to fully elucidate the impact of exposure to complex mixtures of environmental pollutants on hypertension.

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